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Psicoterapia Assistida com MDMA para a Perturbação de Stress Pós-Traumático/ MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder

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Aos meus pais

MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder

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Abstract

Background: Posttraumatic stress disorder is a mental illness with severe implications on patient quality of life and current treatment options, which are mainly psychotherapeutic, have limited results. Recently, MDMA, a highly controversial psychedelic drug, has shown promise as a psychotherapeutic enhancer.

Objective: This review aims to outline existing scientific evidence on the efficacy of MDMA-assisted psychotherapy in treating posttraumatic stress disorder. Other important theoretical knowledge and empirical evidence regarding the drug will also be presented.

Method: Using PubMed as the database, a research was conducted targeting articles written in English about MDMA's use in posttraumatic stress disorder's treatment.

Results: MDMA is still a drug whose complete means of action, albeit known to be mostly related with neurotransmitter metabolism, is not fully understood. Mechanisms involving mood, empathy and arousal modulation, as well as neuroplasticity and long-term personality changes have been proposed as the reason for its properties as a good psychotherapeutic catalyst, but the true explanation remains a matter of scientific debate. Phase 2 clinical trials in patients suffering with posttraumatic stress disorder have so far delivered very promising results: MDMA exposed subjects have shown significantly better results when compared to placebo exposed cases in all but one study, and its application in controlled settings has been considered generally safe, with only one potential serious adverse effect ever reported. Phase 3 clinical trials have been justifiably approved and should address issues regarding the direct comparison with the current preconized treatment options, the optimization of the adverse effects profile, and the reproducibility of the results.

Conclusion: MDMA-assisted psychotherapy is a very appealing new possibility in the treatment of posttraumatic stress disorder. Future studies are necessary for it to become a fully approved therapy.

Keywords: PTSD, MDMA, Psychotherapy

1. INTRODUCTION

1.1. Background

Posttraumatic stress disorder (PTSD) is a common, often chronic, mental illness with severe implications on patient quality of life, and has been increasingly recognized as a public health problem [1].

Treatment options are mainly psychotherapeutic with Prolonged Exposure (PE) therapy being one of the most widely accepted treatments [2]. It is based on a "flooding" mechanism, which requires the patient to re-live his traumatic experiences decoupled from the actual threat, in order induce an extinction of the fear response [3]. Despite being considered the first-line option, PE is very far from being a perfect therapy: remission of symptoms after 40 months is only achieved in around 44% of those undergoing treatment [4], only 32–66% reach a good level of end-state functioning [5] and only a small minority of veteran patients are treated (6.3%) [6] because the emotionally demanding sessions often aggravate the patients' symptoms before they improve [7]. Furthermore, it has high drop-out rates of around 30% [8], which may be explained by the detrimental effects that trauma exhibits on the ability to form trusting interpersonal relationships, therefore affecting the working alliance between the patient and therapist [9], undermining the efficacy of the treatment. Serotonergic agents such as selective serotonin reuptake inhibitors (SSRI) are recommended in treatment guidelines [1], but are mainly used to tackle accompanying comorbid disorders [10], with a large proportion of patients remaining symptomatic [11] and the benefits of its concomitant application with psychotherapy are still matter of debate [1, 12]. Anxiety-reducing drugs were actually proven to be counter-productive in regard to long-term recovery [12].

Recently, ±3,4-Methylenedioxymethamphetamine (MDMA), a highly controversial psychedelic, has shown promise as a psychotherapeutic enhancer in the context of PTSD and has been granted Breakthrough Therapy Designation by the United States of America's Food and Drug Administration (FDA).

1.2. Objective

As phase 3 multi-site trials are currently being conducted, this review aims to outline available scientific evidence on the efficacy of MDMA-assisted psychotherapy in treating PTSD. As such, the main focus will be directed to clinical trials conducted and published to date of the writing of this review. Moreover, other theoretical knowledge and empirical evidence found relevant for a comprehensive understanding of the current scientific landscape on the subject will also be addressed.

2. MATERIALS AND METHODS

Using PubMed as the database, a research was conducted targeting articles written in English about MDMA's use in PTSD's treatment. With the goal of obtaining more information on the pharmacology and psychological effects related to the drug's clinical use, and since MDMA has currently no other thoroughly studied application, a broader, general association between MDMA and psychotherapy was also researched upon. The following query was used: "((MDMA OR 3,4 Methylenedioxymethamphetamine OR N-Methyl-3,4-methylenedioxyamphetamine OR Ecstasy OR Molly) AND (PTSD OR Post-Traumatic Stress Disorder))

OR ((MDMA OR 3,4Methylenedioxymethamphetamine OR N-Methyl-3,4-methylenedioxyamphetamine OR Ecstasy OR Molly) AND (psychotherapy))". The last date of research was 27/12/2019.

The database returned a total 216 articles. One article was excluded for being duplicated. Ten articles were excluded for not being written in English. One hundred and nineteen articles were excluded after reading of the title and abstract for not being related to the theme. The reading of the remaining 86 articles revealed that 35 provided information considered non-relevant or very incomplete and better described in other articles. The 51 remaining articles revealed 16 more articles with relevant information. As result, 67 articles were included in this review, with the results thematically organized to ensure they were depicted in the most intuitive way possible.

3. WHAT IS MDMA

3.1. Historical Background

MDMA is reported to have been firstly synthesized in 1912, although its psychoactive properties were still completely unknown [13]. In 1976, Alexander Shulgin discovered MDMA's psychoactive effect and two years later, alongside with his college David Nichols, released a paper [14] in which their findings were first described. At around the same time, Shulgin introduced the drug to Leo Zeff [15], the first noted psychologist to use MDMA as an adjunct to psychotherapy [16]. The enthusiasm around the therapeutic potential of MDMA grew [17], but just as research was taking of, the recreational use of "ecstasy" (tablets containing MDMA) in the 1980s prompted authorities to schedule the substance as a drug of abuse [18], therefore terminating most of the investigation [19]. By the 1990s, the majority of the studies were focused on the harmful effects of ecstasy consumption [20].

Shortly after MDMA's scheduling, the Multidisciplinary Association for Psychedelic Studies (MAPS) was created and has been the driving force behind most of the investigation on MDMA and other psychedelics. Following 2002's approval of the clinical plan for trials assessing MDMA's use on PTSD [21], serious research has been finally conducted.

3.2. Pharmacology and Effects

MDMA is a racemate composed of equal parts of the *S*(+) and *R*(-) isomers [22]. It penetrates de blood-brain barrier and establishes complex interactions, mainly with neurotransmitter (NT) receptors. Effects usually peak 2h after administration and the drug's half-life elimination revolves at around 8-h [23]. MDMA and its metabolites are primarily cleared by cytochrome P450 (CYP), catechol-O-methyltransferase (COMT), glucuronidation, or sulfation isoenzymes, so patients with genetic polymorphisms affecting these enzymes or those taking drugs that affect CYP or COMT may have an increased risk of unpredictable or harmful effects related to its consumption [24]. It is also a potent CYP2D6 inhibitor, leading to potential interactions with CYP2D6 substrates like SSRI's [24].

Even though MDMA's complete mechanism of action is not fully understood, its distinct effects are known to be primarily related to an impact on serotoninergic transmission. This is due to its properties as a nonclassical serotonin transporter (SERT) substrate, inducing non-exocytotic serotonin (5-HT) release, by

triggering a reversal of the normal transporter flux [25]. In addition, it also blocks 5-HT reuptake to produce a dual extracellular 5-HT raising mechanism [22]. Resulting acute cognitive effects include enhanced mood and well-being; happiness; physical and mental relaxation; increased emotional sensitivity and responsiveness; increased self-confidence; positively altered evaluation of the self while decreasing concerns about negative evaluation by others, heightened openness; extroversion and sociability; the feeling of closeness to other people; as well as slight (visual, auditory, and tactile) changes in perception and anxiolysis [26-29]. This unique combination has been defined as a "pro-social syndrome" [28], which has led some authors to state that MDMA should not be confined to its traditional designation as a psychedelic amphetamine, but belong to a new class of psychoactive drugs called "entactogens" [30]. Since 5-HT acts on more than a dozen different receptor subtypes, the task of elucidating which of them might be related to each specific effect is rather complicated [31].

In addition, other NT are also implicated in MDMA's acute effect, mainly Norepinephrine (NE) and Dopamine (DA). This is due to its effects on the NE transporter (NET) and DA transporter (DAT), blocking both NT's reuptake and stimulating their release similar to what happens with 5-HT [31]. Higher extracellular NE concentrations have been associated with stimulant-like effects [32], while elevated DA transmission might be related to the positive mood modulation [33], but also the deleterious effects like hyperthermia and abuse potential [34, 35].

Furthermore, MDMA also induces neurohormonal effects, the most important being the stimulation of oxytocin release. This is thought to inhibit the autonomic fear response and centrally potentiate complex social behaviors involving pair-bonding, sex, affiliative behavior and pro-social feelings [36]. Another relevant effect is the potentiation of cortisol release, which relates to elevated mood, increased energy and reduced fatigue [37].

4. MDMA AND PSYCHOTHERAPY

MDMA's utility as psychotherapeutic adjuvant starts with its appealing pharmacokinetic profile, since the average duration of substance-assisted treatment sessions coincides with its half-life (around 8h) [38].

Extensive research has been conducted on both the exact properties that might make MDMA a useful tool in the context of PTSD's treatment, and on the drug's potentially negative effects on exposed individuals.

4.1. Benefits

The reason why MDMA is an efficient psychotherapeutic adjuvant in PTSD still remains a matter of research, with multiple proposed mechanisms that, even though likely interconnected, will be presented in two separated topics for the sake of better explanation.

4.1.1. Short-term benefits

As previously mentioned, the "flooding" process, in which PE therapy in PTSD is based on, requires the patient to relieve the actual memory, possibly leading to an acute elevation of the very own symptoms the

therapy wishes to reduce. This fine line between treating and hurting is one of the main reasons why PE shows limited results, and here is where pharmacological enhancement by MDMA comes to play by. [3, 12]

Firstly, while the improved mood state has a predictable positive modulation effect on the present perception of the memories, MDMA might also have a selective effect on emotional memory retrieval, altering the recollection of details specifically associated with negative and positive stimuli [39], therefore attenuating the intensity of the experienced fear during the session and allowing for a better trauma exploration.

Furthermore, since trauma impairs the patient's ability to form a trusting relationship with the therapist, it is hypothesized that the heightened sociability allows a better "working alliance" [23]. In fact, evidences shows that MDMA-exposed individuals produce greater numbers of empathic (regarding others' emotions), entactic (requesting or appreciating physical touch), and ensuic (describing a change in their sense of themselves) utterances in clinical settings [40]. This effect might be explained by an altered conceptualization of "social reward" (placing more emphasis on the direct relationship with interacting partners) [41], a decrease in the perception of social rejection [42] and a selective modification of the socially-related stimuli processing, slowing the perception of negative emotions, and potentiating the response to positive ones, leading to an increase in the comparative value of social contact and closeness with others, as opposed to non-social stimuli [43, 44].

Finally, MDMA's elevation of DA and NE, as well as the induction of cortisol release, are thought to produce a combined stimulant effect that increases patients' motivation to engage in therapy without feeling overwhelmed by the arising emotions [45], setting up an "optimal arousal zone" where patients are appropriately alert and motivated to engage in the psychotherapeutic process, but not overly stimulated as to be hypervigilant [5].

4.1.2. Long-term benefits

Heightened fear response to environmental stimuli is shown to be reflected in neuroimaging as hyperactivity in the amygdala and hypoactivity in the prefrontal cortex [36]. Recent functional magnetic resonance imaging (fMRI) studies have shown that, in healthy volunteers, MDMA causes a modulation of spontaneous brain activity resulting in augmented activations in response to favorite memories in some regions, and attenuated activations to worst memories in others [46, 47]. The alteration of the crosstalk between these areas could be the neural correlate of an higher mismatch between the memory trace and present happenings experienced by MDMA exposed patients which, in the event of a potentiation of neuroplasticity, may allow for new and less stressful emotional content to be overlaid on these circuits, modifying the existing memory, and amplifying both treatment's short and long-term therapeutic effects [36, 48].

In a mouse model trial, MDMA exposure has shown to enhance both long-term fear extinction and the transcription of brain-derived neurotrophic factor (BDNF), a compound that plays a crucial role in promoting hippocampal synaptic plasticity and regulating memory reconsolidation [49], which might allow for older memories to be "reconfigured". Interestingly, the same authors reported in a later study that chronic

and acute administration of a SSRI blocked this positive effect on fear memory extinction, a relevant finding given the large number of PTSD patients currently treated with SSRI drugs [50]. However, a recent trial conducted using Dark Agouti rats as opposed to mice, reported MDMA to be more prone to inhibit rather than enhance fear-extinction learning [51], an inconsistency that accentuates the need for more research. Nevertheless, genetic expression in the same Dark Agouti rats strain seems to support this mechanism, as a single dose of MDMA has been reported to upregulate various gene sets related to neuroplasticity and synaptic formation/reorganization in the frontal cortex, while downregulating genes related to memory and cognition in the hippocampus [52].

Another mechanism possibly related with the long-term benefits is based on the therapy's effect on personality, since evidence suggests that MDMA assisted-psychotherapy may induce long-term changes in patients' traits associated with trauma, such as a boost in openness (increased seeking out of new experiences, being more prone to self-examination, more imaginative, and more sensitive to inner feeling and the feelings of others [53], an hypothesis which indicates that MDMA's clinical application may be able to shift aspects of personality assumed to be relatively stable constructs throughout much of adulthood [53, 54].

4.2. Potentially Harmful Effects

Various deleterious effects related to "Ecstasy's" recreational usage have been reported in the literature. Though these effects might, at first, seem important for the aim of this paper, since the vast majority of research concerning "Ecstasy" appears to be inapplicable for the strict establishment of risks concerning the potential usage of MDMA in clinical settings due to purity issues [26], uncontrolled polydrug consumption [55], and environmental differences [27], the two concepts are not considered interchangeable and a review on "Ecstasy" will not be conducted.

Reported negative psychological effects demonstrated in human studies with MDMA include depersonalization; dissociative symptoms; lack of energy; depression; sleep disturbances; and transient deficits in immediate and delayed recall, working memory, selective attention and associative memory [22]. Furthermore, some evidences of neurobiological damage have been reported in rat models, such as an oxidative stress-related persistent decrease in 5-HT neurotransmission [22], and, in previously stressed subjects, a significant downregulation of gene categories related to tissue regeneration, axon ensheathment, and cytokine receptor interaction [56]

More theoretical concerns are also worth mentioning. Firstly, since the main mode of operation of MDMA's assisted psychotherapy consists on stimulating the release of difficult and stressing feelings and memories, then there might be some clinical scenarios in which MDMA-induced experiences may prove difficult to control and potentially more stress-inducing to the patient, especially if the therapists are inexperienced [57]. Furthermore, patients might misattribute therapeutic gains to medication, minimizing the importance of maintaining the improvements through psychological changes, leading to a greater relapse risk [26]. This relates to the potential risk of patients seeking illicit supplies of MDMA after experiencing therapies with good results, which naturally accommodates the psychological consequences inherent to all non-medically advised psychoactive drug consumption. In addition, psychiatrically vulnerable patients may

also be in danger of experiencing unexpected and undesired symptoms when exposed to a psychedelic drug [57].

5. CLINICAL TRIALS

The most widely accepted guide for conducting MDMA-assisted psychotherapy was published by MAPS [58] and is regularly updated. It follows the usual framework normally applied in other Psychedelic-assisted psychotherapies (PAP), generally including drug-free sessions before (preparatory) and/or after (integrative) drug sessions [59].

All recent MDMA-assisted psychotherapy trials were conducted meeting rigorous standards for drug development, regulated by the FDA or equivalents, and overseen by Institutional Review Boards (IRBs). Moreover, in the United States, due to the Schedule 1 status of MDMA, compliance with the Drug Enforcement Administration (DEA) and state-level controlled substance review committees is required, placing these studies in the most regulated area of drug development [60].

In all trials, the primary outcome measure was the variation in CAPS (Clinician-Administered PTSD Scale), with clinical response being generally defined as a >30% decrease on the score. Most studies included two stages, with the second one consisting of an open-label crossover, in which control subjects also had the opportunity to receive an active dose of MDMA [10, 23, 54, 61]. Long-term follow-ups (LTFU), generally up to one year, intended to evaluate the persistency of the effects over time were also performed. Neurocognitive testing, blood pressure and temperature monitoring were used to assess adverse effects.

To this day, 5 clinical trials testing MDMA's efficacy as a psychotherapeutic adjuvant in the context of PTSD's treatment have been conducted.

5.1. Bouso et al. (2008): [62]

The first fully approved placebo-controlled clinical trial. The main objective was to assess the safety of a single psychotherapy session on 29 chronic PTSD sufferers using a wide range of symptom and comorbidity scales.

Political pressure resulted in only 6 subjects being treated before the sudden termination of the study. Despite the abrupt conclusion, no adverse effects were reported.

5.2. Mithoefer et al. (2011): [23]

Published in 2011, this was the first randomized, double-blind, placebo-controlled trial conducted in the United States. Twenty subjects with chronic refractory posttraumatic stress disorder were randomly assigned to psychotherapy with an inactive placebo, or with a full 125mg dose of MDMA (with the possibility of an additional 65mg 2h later).

Decreases in CAPS scores from baseline and rates of clinical response were significantly greater for the group that received MDMA than for the placebo group (67.8% versus 25.8%), with the latter showing similar magnitude improvements after the open-label crossover. There were no reports of serious drug-related adverse events or neurocognitive effects. The LTFU [63] concluded there were no statistical differences

between mean CAPS scores at the given time and those obtained at study exit, which indicated that the benefits persisted over time.

Despite the small sample size, low gender and ethnic differences between patients (majority female and all Caucasian), and the inefficacy of the double-blinding since both the patients and the therapists could tell if the subject had taken MDMA, this was the first study that firmly highlighted the therapeutic potential of the drug as a psychotherapy catalyst.

5.3. Oehen et al. (2013): [10]

A few years later, in Switzerland, Oehen *et al.* (2013) conducted the first active placebo trial. The study enrolled 12 patients with treatment-resistant PTSD for therapy with either low-dose (25 mg, plus 12.5 mg as supplemental dose) or full-dose MDMA (125 mg, plus 62.5 mg as supplemental dose). The Posttraumatic-Diagnostic Scale (PDS), a self-reporting measure to access the presence of PTSD symptoms, was used as a secondary outcome measure.

After stage 1, a significant PDS improvement was reported in the full-dose group relatively to the active placebo group, however the results were not as impressive as those published 2 years earlier by Mithoefer *et al.* (2011) regarding CAPS reduction, with no findings of statistically significant differences between the two groups. Nevertheless, clinical response was reported in 50% of the subjects in the full-dose group. Interestingly, three sessions were reported to exhibit significantly superior effects than only two.

The active placebo improved the blinding when compared to the inactive one used in Mithoefer's study but turned out to be less well tolerated psychologically in three of the control subjects, due to what the authors refered to as a "state of partial activation", consisting of spontaneous recall, but without maximum fear reduction. Despite this counter-therapeutic effect, no serious adverse reactions were reported in any group.

Persistent benefits were once again reported in the LTFU, however some subjects had begun a new therapy during that period, which undermines the conclusions about the long-term effects.

5.4. Mithoefer et al. (2018): [54]

More recently, Mithoefer *et al.* (2018) published another trial, this time including 26 military veterans and first responders with CAPS scores >50, randomized into three different dose groups: an active placebo control of 30mg, a 75mg group and a 125mg group.

Contrary to the Oehen study, the trial showed higher MDMA doses to have very significant beneficial results when compared to lower ones, both at the primary endpoint, in which the 125 mg and 75 groups had mean changes in CAPS of –70.8% and –49.4% versus –13.0 observed in the 30 mg group, and after the open-label crossover, in which the original 30mg group showed similar improvements. This time, no counter-therapeutic effect in the low-dose groups was verified.

Despite the treatment being once again reported as generally well tolerated, one severe cardiac adverse effect possibly related to MDMA's administration was described. Even though it was conveniently

detected, and the subject recovered without evidence of any vascular or structural cardiac disease, it raises some concerns regarding the drug's cardiovascular safety.

After the LTFU the gains were clearly maintained, not only in terms of CAPS score (mean CAPS score of 38.8 versus 87.1 at baseline), but also in the personality traits associated with trauma, reinforcing the hypothesis that MDMA clinical application might be capable of long-term personality changes.

5.5. Ot'alora et al. (2018):[61]

The most recent study was conducted by Ot'alora *et al*. (2018) and was the first to assess the efficacy and safety of MDMA-assisted psychotherapy across multiple therapy teams, with subjects randomized into two active dose groups of 100mg and 125mg, and one active placebo group of 40mg.

CAPS score reduction was greater in the active groups, even with different therapy teams, an important finding giving that multi-site Phase 3 trials are due to begin shortly. This time, however, outcomes were analyzed according to intent-to-treat (ITT) versus per-protocol (PP) method, and statistical significance was only attained in the latter set. This indicates that, not only in this study but also in the previous ones, withdrawals may have an important implication on the overall outcome. Three sessions were found to be more efficient than two in the 100 and 125mg groups, but not in the 40mg group. No significant adverse effect was reported.

The gains were maintained over the LTFU after all groups had received active doses of MDMA, with 76% of all the individuals not meeting the criteria for a PTSD diagnosis, which is consistent with previous findings regarding the therapy's long-term benefits.

6. DISCUSSION

Novel therapy research, especially for conditions, like PTSD, whose approved options show limited results, is always welcome. Nonetheless, reported clinical benefits that seem too good to be true must be looked upon with a careful balance between enthusiasm and skepticism, a stance that may prove particularly hard to maintain when research is conducted on substances with a history as controversial as psychedelic drugs. Furthermore, their suggested ability to perturb consciousness in a way that a single acute exposure might elicit immediate and lasting changes to the patients' psyche [64] may raise relevant ethical questions regarding their clinical use. However, this also means they are a compelling tool for understanding the connectivity of the brain and could represent a new paradigm in the way medicine understands and treats psychiatric illnesses [64]. MDMA-assisted psychotherapy for PTSD's seems to capitalize on this exact property, as treatment does not simply symptomatically "paper over" the cracks of trauma, but tackles it's very own neuronal foundation [65].

While MDMA's pharmacological properties and mechanisms of action still need additional research to be completely understood, clinical trials have supported the safety of MDMA in controlled settings, and have been consistent with the imperative need to completely separate its concept from that of "ecstasy" [10, 23, 54, 61, 62]. All trials but one [10] reported significant clinical efficacy, which legitimizes future research and the Breakthrough Therapy Designation granted by the FDA. So far, it appears the current full-dose of

125mg is the most efficient application, with supplemental dosage not showing consistent benefits and lesser measures sometimes exhibiting deleterious effects [10]. Three therapeutic sessions have, in some cases, demonstrated better results than two [10, 61]

A preliminary meta-analysis published in 2016, thus including only 3 out of the 5 trials conducted so far, reported that MDMA-assisted psychotherapy was superior to PE when evaluated by clinician-observed outcomes, by patient self-report outcomes and by drop-outs [66]. However, the type of psychotherapy currently administered with MDMA is none of the empirically supported exposure-based treatments for PTSD [1]. Therefore, a direct comparison between MDMA-assisted psychotherapy and the standard-of-care PE with SSRI therapy is still lacking and should be addressed on subsequent clinical trials [24].

The fact that one of the trials demonstrated the efficacy of the therapy in war veterans, one of the most treatment-resistant patient groups, is also encouraging. Nevertheless, as demonstrated by the most recent study [61], drop-out rates, a central reason for the failure of current psychotherapeutic options, have also shown to influence the effectiveness of MDMA-assisted psychotherapy, an issue that must be further scrutinized on future studies.

Despite the overall safety profile of clinical MDMA's application looking relatively stable throughout all trials, the serious cardiac event verified in one of them [54] raises important questions concerning its hemodynamic effects on patients suffering from cardiovascular conditions.

Furthermore, patients receiving SSRIs, which are commonly used in psychiatry and that pharmacologically block the effects of MDMA, might experience lackluster results and even some undesired effects, like those observed in the low-dose group of the Oehen *et al.* (2013) trial. In fact, lower MDMA doses have recently been reported to have less "good drug effects" than higher ones [67]. This turns the risk-benefit evaluation of removing the SSRI to potentiate the therapy versus maintaining it to prevent the relapse of depressive symptoms, a focal point of patient assessment. Additionally, MDMA's effect on CYP, COMT and CYP2D6 must also be taken into consideration, since it may underlie potentially unpredictable effects.

A new possible way to minimize negative effects based on MDMA's racemic nature has been proposed. Findings suggest that *R*(-)-MDMA may be a clinically superior drug in comparison to the commonly used racemic MDMA, maintaining the therapeutic effects while reducing the adverse ones [34, 35]. This new possibility should be kept in mind for future trials.

Also noteworthy is the fact that nearly all clinical trials so far have been conducted with the direct involvement of MAPS personnel. The preponderance of this association in the drug's study is undeniable, and, without its existence, MDMA would most certainly still be regarded as nothing more than the central compound of a street drug. However, and since the only study that took part outside the United States without their firsthand involvement ended up with significantly less thrilling results [10], further investigations should have the freedom to analyze and report their conclusions without the intervention of MAPS, for the sake of better and stronger scientific evidence.

CONCLUSION

MDMA-assisted psychotherapy surely is a promising new therapeutic option for PTSD. Current findings are consistent with its overall safety and the outcome results completely justify the conduction of more research. However, issues regarding its direct comparison to current preconized treatment options, optimization of the adverse effects profile, and reproducibility of the results still need to be attended so it can become a fully approved treatment. Phase 3 clinical trials will provide invaluable and decisive information on the matter.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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None.

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ANEXOS

Normas da Revista "Current Clinical Pharmachology"

MANUSCRIPT PREPARATION

The manuscript should be written in English in a clear, direct and active style. All pages must be numbered sequentially, facilitating in the reviewing and editing of the manuscript.

MICROSOFT WORD TEMPLATE

It is advisable that authors prepare their manuscript using the template available on the Web, which will assist in preparation of the manuscript according to Journal's Format.

SECTIONS IN MANUSCRIPTS

Manuscripts submitted for research and review articles in the journal should be divided into the following sections:

- Title;
- Title Page;
- Structured Abstract;
- Graphical Abstract;
- Keywords;
- Text Organization;
- Conclusion;
- List of Abbreviations (if any);
- Consent for Publication;
- Conflict of Interest;
- Acknowledgements;
- References;
- Appendices;
- Figures/Illustrations (if any);
- Chemical Structures (if any);
- Tables (if any);
- Supportive/Supplementary Material (if any).

Title

The title of the article should be precise and brief and must not be more than 120 characters. Authors should avoid the use of non-standard abbreviations and question marks in titles. The first letter of each word should be in capital letters except for articles, conjunctions and prepositions.

Authors should also provide a short 'running title'. Title, running title, byline, correspondent footnote and keywords should be written as presented in original manuscripts.

Title Page

Title page should include paper title, author(s) full name and affiliation, corresponding author(s) names complete affiliation/address, along with phone, fax and email.

Structured Abstract

The abstract of an article should be its clear, concise and accurate summary, having no more than 250 words, and including the explicit sub-headings (as in-line or run-in headings in bold). Use of abbreviations should be avoided and the references should not be cited in the abstract. Ideally, each abstract should include the following sub-headings, but these may vary according to requirements of the article:

- Background;
- Objective;
- Method;
- Results;
- Conclusion.

Graphical Abstract

A graphic should be included when possible with each manuscript for use in the Table of Contents (TOC). This must be submitted separately as an electronic file (preferred file types are EPS, PDF, TIFF, Microsoft Word, PowerPoint and CDX etc.). A graphical abstract, not exceeding 30 words along with the illustration, helps to summarize the contents of the manuscript in a concise pictorial form. It is meant as an aid for the rapid viewing of the journals' contents and to help capture the readers' attention. The graphical abstract may feature a key structure, reaction, equation, etc. that the manuscript elucidates upon. It will be listed along with the manuscript title, authors' names and affiliations in the contents page, typeset within an area of 5 cm by 17 cm, but it will not appear in the article PDF file or in print.

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6 to 8 keywords must be provided. Choose important and relevant keywords that researchers in your field will be searching for so that your paper will appear in a database search. In biomedical fields, MeSH terms are a good 'common vocabulary' source to draw keywords from https://www.nlm.nih.gov/mesh/meshhome.html.

Text Organization

The main text should begin on a separate page and should be divided into title page, abstract and the main text. The text may be subdivided further according to the areas to be discussed, which should be followed by the List of Abbreviations (if any), Conflict of Interest, Acknowledgements and Reference

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SECTION HEADINGS

Section headings should be numbered sequentially, left aligned and have the first letter capitalized, starting with the introduction. Sub-section headings however, should be in lower-case and italicized with their initials capitalized. They should be numbered as 1.1, 1.2, *etc*.

INTRODUCTION

The Introduction section should include the background and aims of the research in a comprehensive manner.

MATERIALS AND METHODS

This section provides details of the methodology used along with information on any previous efforts with corresponding references. Any details for further modifications and research should be included.

EXPERIMENTAL

Repeated information should not be reported in the text of an article. A calculation section must include
experimental data, facts and practical development from a theoretical perspective.

RESULTS

Results should be precise.

DISCUSSION

This should explore the significance of the results of the work, present a reproducible procedure and emphasis the importance of the article in the light of recent developments in the field. Extensive citations and discussion of published literature should be avoided.

The Results and Discussion may be presented together under one heading of "Results and Discussion". Alternatively, they may be presented under two separate sections ("Results" section and "Discussion" Sections). Short sub- headings may be added in each section if required.

CONCLUSION

A small paragraph summarizing the contents of the article, presenting the final outcome of the research or proposing further study on the subject, may be given at the end of the article under the Conclusion section.

Greek Symbols and Special Characters

Greek symbols and special characters often undergo formatting changes and get corrupted or lost during preparation of manuscript for publication. To ensure that all special characters used are embedded in the text, these special characters should be inserted as a symbol but should not be a result of any format styling (Symbol font face) otherwise they will be lost during conversion to PDF/XML.

Authors are encouraged to consult reporting guidelines. These guidelines provide a set of recommendations comprising a list of items relevant to their specific research design. Chemical equations, chemical names, mathematical usage, unit of measurements, chemical and physical quantity & units must conform to SI and Chemical Abstracts or IUPAC.

All kinds of measurements should be reported only in International System of Units (SI).

Appendices

In case there is a need to present lengthy, but essential methodological details, use appendices, which can be a part of the article. An appendix must not exceed three pages (Times New Roman, 10 point fonts, 900 max. words per page). The information should be provided in a condensed form, ruling out the need of full sentences. A single appendix should be titled APPENDIX, while more than one can be titled APPENDIX A, APPENDIX B, and so on.

Supportive/Supplementary Material

We do encourage to append supportive material, for example a PowerPoint file containing a talk about the study, a PowerPoint file containing additional screenshots, a Word, RTF, or PDF document showing the original instrument(s) used, a video, or the original data (SAS/SPSS files, Excel files, Access Db files etc.) provided it is inevitable or endorsed by the journal's Editor.

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If abbreviations are used in the text either they should be defined in the text where first used, or a list of abbreviations can be provided.